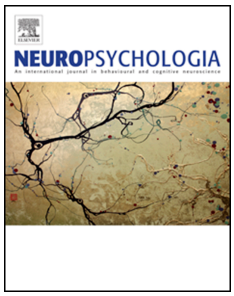
Article:
Krieger-Redwood, Katya Melanie, Wang, Hao-Ting, Poerio, Giulia et al. (4 more authors) (2019) Reduced Semantic Control in Older Adults is Linked to Intrinsic DMN Connectivity. Neuropsychologia. ISSN 0028-3932

https://doi.org/10.1016/j.neuropsychologia.2019.107133

Accepted Manuscript



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PII: S0028-3932(19)30170-8

DOI: https://doi.org/10.1016/j.neuropsychologia.2019.107133

Article Number: 107133

Reference: NSY 107133

To appear in: *Neuropsychologia*

Received Date: 1 February 2019

Revised Date: 27 May 2019

Accepted Date: 1 July 2019

Please cite this article as: Krieger-Redwood, K., Wang, H.-T., Poerio, G., Martinon, Lé.M., Riby, L.M., Smallwood, J., Jefferies, E., Reduced semantic control in older adults is linked to intrinsic DMN connectivity, *Neuropsychologia* (2019), doi: https://doi.org/10.1016/j.neuropsychologia.2019.107133.

Reduced Semantic Control in Older Adults is Linked to Intrinsic DMN Connectivity

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Abstract

Ageing provides an interesting window into semantic cognition: while younger adults generally outperform older adults on many cognitive tasks, knowledge continues to accumulate over the lifespan and consequently, the semantic store (i.e., vocabulary size) remains stable (or even improves) during healthy ageing. Semantic cognition involves the interaction of at least two components – a semantic store and control processes that interact to ensure efficient and context-relevant use of representations. Given older adults perform less well on tasks measuring executive control, their ability to access the semantic store in a goal driven manner may be compromised. Older adults also consistently show reductions in intrinsic brain connectivity, and we examined how these brain changes relate to age-related changes in semantic performance. We found that while older participants outperformed their younger counterparts on tests of vocabulary size (i.e., NART), younger participants were faster and more accurate in tasks requiring semantic control, and these age differences correlated with measures of intrinsic connectivity between the anterior temporal lobe (ATL) and medial prefrontal cortex (mPFC), within the default mode network. Higher intrinsic connectivity from right ATL to mPFC at rest related to better performance on verbal (but not picture) semantic tasks, and older adults showed an exaggerated version of this pattern, suggesting that this within-DMN connectivity may become more important for conceptual access from words as we age. However, this appeared to be at the expense of control over semantic retrieval – there was little relationship between connectivity and performance for strong associations in either group, but older adults with stronger connectivity showed particularly inefficient retrieval of weak associations. Older adults may struggle to harness the default mode network to support demanding patterns of semantic retrieval, resulting in a performance cost.

Keywords: semantic, DMN, ageing, control

Introduction

Ageing is generally associated with declines in cognition and corresponding changes in brain structure and function. Brain activity in older adults differs to that of younger adults, and this relates to their poorer performance on cognitive tasks (Grady, 2012; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Spreng, Wojtowicz, & Grady, 2010). Even in the absence of extrinsic demands, older individuals have been consistently shown to have reduced brain connectivity (Andrews-Hanna et al., 2007; Grady, Sarraf, Saverino, & Campbell, 2016). However, in contrast to this general effect of reduced cognitive performance – including on tests of episodic and working memory, and executive control – semantic memory is thought to remain relatively protected from age-related cognitive decline (Braver & West, 2008). In particular, older adults perform better than younger individuals on tests of vocabulary, reflecting the fact that knowledge is acquired over a lifetime (Hoffman, 2018b; Salthouse, 2004; Verhaeghen, 2003). Despite this preservation of the semantic store, use of conceptual information in a goal-driven fashion might be less efficient in older adults, given their well-documented executive deficits.

Semantic cognition – the appropriate use of semantic knowledge to drive thoughts and behaviour appropriate to the circumstances – is thought to involve the interaction of at least two separable components: conceptual representations in long-term memory, and control processes that flexibly shape the retrieval of information to suit the context or current goals. These distinct neurocognitive components show dissociations in the neuropsychological and neuroimaging literature. For instance, patients with semantic aphasia have an intact store of knowledge, but they have deficits in the flexible use of conceptual information, following lesions to left inferior frontal gyrus and/or posterior middle temporal gyrus. Consequently, these patients are highly sensitive to task demands within the semantic domain, and show strong effects of cues and miscues that reduce or increase the need for internal constraint over conceptual retrieval. The left inferior frontal gyrus and/or posterior middle temporal gyrus are thought to form a 'semantic control network', which supports the flexible application of knowledge. Indeed, co-activation of these key regions has been observed across a wide-range of control-demanding semantic tasks, involving semantic ambiguity, strong distractors and the retrieval of weak as opposed to strong associations (Davey et al., 2015; Noonan, Jefferies, Visser, & Lambon Ralph, 2013).

In contrast, patients with semantic dementia show degradation of conceptual knowledge within the semantic store, associated with atrophy of the ventral anterior temporal lobes (ATL) bilaterally. As a consequence, SD patients are highly consistent in the concepts that they can retrieve, irrespective of the control demands of semantic tasks, and they are relatively insensitive to cues. The ATL is thought to act as a 'semantic hub' that computes coherent concepts across multiple feature types, such as vision, audition, language, action and emotion (Jefferies, 2013; Jefferies, Baker, Doran, & Lambon Ralph, 2007; Jefferies & Lambon Ralph, 2006; Pobric, Jefferies, & Ralph, 2010; Pobric, Lambon Ralph, & Jefferies, 2009; Visser, Jefferies, Embleton, & Lambon Ralph, 2012; Visser, Jefferies, & Lambon Ralph, 2009; Visser & Lambon Ralph, 2011). The ATL has a pattern of intrinsic connectivity that is distinct from semantic control regions; it shows stronger coupling to elements of the default mode network (DMN), and it has been suggested that these regions in combination support relatively 'automatic' patterns of conceptual retrieval in which long-term conceptual representations are well-aligned with task requirements (since dominant associations or the strongest semantic features are required; Humphreys, Hoffman, Visser, Binney, & Lambon Ralph, 2015; Murphy et al., 2018; Murphy et al., 2017).

There has been little research on the effect of ageing on these separable components of semantic cognition, namely conceptual representation (linked to ATL) and control (linked to left

inferior frontal gyrus). However, there is some indication that older adults may have specific difficulty controlling semantic retrieval; for example, older adults have increased tip-of-the-tongue states compared with younger adults (Shafto, Stamatakis, Tam, & Tyler, 2009), suggesting that their retrieval processes may be compromised. Furthermore, a recent study found that while older adults had a larger vocabulary than younger adults, they performed less well on tasks that required semantic selection (and this was correlated with non-semantic executive ability; Hoffman, 2018a; Hoffman, 2018b; Hoffman, Loginova, & Russell, 2018).

To date, there have been few studies of the neural correlates of this age-related dissociation between semantic representation and control. Ageing is thought to affect patterns of intrinsic connectivity and task-induced BOLD responses across multiple networks relevant to semantic cognition (e.g., DMN; executive network; Grady, 2012; Spreng & Turner, 2018). A recent meta-analysis of neuroimaging studies of semantic cognition by Hoffman and Morcom (2018) found that activation across networks was broadly similar in older and younger participants. However, when older participants performed less well on semantic tasks, they showed decreased activation in the semantic control network (particularly left inferior frontal gyrus, pMTG and inferior parietal cortex), and increased activation in the right hemisphere and MDN regions typically associated with domain general executive processing. More broadly, when performing executively-demanding tasks, older adults show stronger recruitment bilaterally, although this does not necessarily benefit their performance (Cabeza, 2002). In addition to increased task-induced activation (Morcom, Li, & Rugg, 2007; Spreng et al., 2010; Townsend, Adamo, & Haist, 2006), they also show reduced task-related deactivation of default mode network regions (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Esposito et al., 2008; Grady et al., 2010; Grady et al., 2006; Lustig et al., 2003; Miller et al., 2008; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Sambataro et al., 2010) and reduced connectivity within the core of this network at rest (Allen et al., 2011; Andrews-Hanna et al., 2007; Grady et al., 2016; Hedden et al., 2009). In this way, they show less differentiation between networks (Morcom et al., 2007), and less flexible and efficient switching between normally anti-correlated patterns of neural response (Clapp, Rubens, Sabharwal, & Gazzaley, 2011).

The current study examines how intrinsic brain connectivity relates to changes in semantic cognition during ageing. Older adults might show different patterns of connectivity at rest, both from seeds within semantic control regions (e.g. inferior frontal gyrus) and from left and right ATL. This age-related variation in connectivity could predict individual differences in specific components of semantic cognition in different ways in older and younger adults. In younger adults, the efficiency of semantic retrieval might relate to stronger intrinsic connectivity within semantically-relevant DMN regions, as well as flexible coupling between these regions and the semantic control network (Krieger-Redwood et al., 2016), potentially facilitated by the broad separation of anti-correlated networks (Vatansever et al., 2017). Given that older adults have difficulty deactivating elements of DMN to support demanding tasks, they might not benefit in the same way from greater connectivity within DMN. They might also show dissolution of the semantic control network.

To test these hypotheses, we acquired resting-state scans and behavioural data on different measures of semantic cognition, in older and younger adults. We used a widely adopted manipulation of semantic control that required participants to retrieve associations between items that were either strong or weak (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011). Weak associations are thought to require more control since the link between concepts is non-dominant within the semantic store; this makes it more difficult to identify the target and inhibit the distractors. We also considered the effect of modality on semantic processing. Although

both the semantic hub and control processes are thought to heteromodal – supporting both verbal and non-verbal semantic tasks – there are thought to be graded differences between the hemispheres: left ATL is thought to have stronger connectivity to other left-lateralised language areas, while right ATL may play a greater role in processing pictures (Lambon Ralph, Hoffman, & Rice, 2015; Rice, Hoffman, & Lambon Ralph, 2015). Older individuals have been shown to exhibit less hemispheric lateralisation (Cabeza, 2002), suggesting they may potentially show differences between word and picture semantic tasks.

Method

Participants

We had two groups of participants, healthy older adults (N = 39; 22 women; mean age = 66, range = 32: 55-87), recruited through opportunity sampling; and healthy younger adults (N = 41; 32 women; mean age = 20; range = 5: 18-23) who were undergraduate students recruited at the University of York. Participants were financially compensated for their time. All participants were right handed, native English speakers, with normal/corrected hearing and vision. Any participants with neurological or psychiatric disorders were excluded from the study. Older participants completed the Mini-Mental State Examination, (MMSE; Folstein et al., 1975) to ensure that they did not have dementia or mild cognitive impairment (threshold: score ≥ 26/30). This study was approved by the University of York Neuroimaging Centre Ethics Committee and conformed to the principles of the Declaration of Helsinki. All participants were briefed in full, provided written informed consent, and were free to withdraw from the study at any time. The participants took part in a larger exploration of the effect of ageing on mind-wandering (Martinon et al., under review). While mind-wandering lies outside the scope of this investigation, the same neuroimaging and neuropsychological data were acquired across the two projects.

Tasks

All participants completed semantic association tasks, that differed either in modality (word vs pictures) or strength of association (weak or strong; Figure 1). These 3-alternative forced choice (3-AFC) tasks consisted of a probe and three choices, one of which was the target (e.g., canoe – paddle, toast, ball). For the manipulation of association strength, the degree of difficulty related to the distance of association between the semantic items (i.e., strong: crossbow- target; weak: banjo-radio). These trials consisted of a picture probe and three written answer choices below (Figure 1). The modality manipulation probed semantic associations in a similar way, but contrasted verbal judgements (i.e., written probes and targets) and picture judgements (i.e. pictorial probes and targets (Figure 1). Accuracy on these tasks was relatively high, but did differ significantly between the two groups (except for the word task; Table 1).

	Strong		Weak		Word		Picture	
	Young	Old	Young	Old	Young	Old	Young	Old
RT	1235 (28)	1575 (46)	1724 (37)	2039 (49)	1439 (27)	1674 (44)	1199 (32)	1606 (49)
	t(64) = -6.3, p < .001		t(73) = -5.1, p < .001		t(65) = -4.5, p ≤ .001		t(67) = -7, p < .001	
ACC	0.97	0.91	0.78	0.68	0.91	0.88	0.93	0.85
	t(45) = 3.6, p ≤ .001		t(52) = 3.7, p < .001		t(56) = 1.1, p = .26		t(46) = 3.2, p = .003	

Table 1: RT for each age group and task, standard error in parentheses; ACC for each age group. Two-tailed independent samples t-tests; corrected for Levene's test. All significant t-tests survive Bonferroni correction (p = .013).

Procedure

Participants underwent lab-based behavioural testing sessions, two hours in duration, on two consecutive days. They performed a large battery of computer-based tasks, including the semantic association tasks, the National Adult Reading Test (NART), a shortened version (18 questions) of the Raven's Advanced Progressive Matrices (RAPM), as well as measures unrelated to this study, such as those related to mind-wandering, inhibition, episodic memory, etc (Martinon et al., under review).

Image Acquisition

Structural and functional (i.e., resting state) MRI scans were acquired using a 3T GE HDx Excite MRI scanner utilising an eight-channel phased array head coil (GE) tuned to 127.4 MHz, at the York Neuroimaging Centre, University of York. All structural MRI acquisition was based on a T1-weighted 3D fast spoiled gradient echo sequence (TR = 7.8 s, TE = minimum full, flip angle= 20°, matrix size = 256 x 256, 176 slices, voxel size = 1.13 x 1.13 x 1 mm). Whole brain resting-state functional MRI activity was recorded using single-shot 2D gradient-echo-planar imaging (TR = 3 s, TE = minimum full, flip angle = 90°, matrix size = 64 x 64, 60 slices, voxel size = 3 x 3 x 3 mm3, 180 volumes). Co-registration of subject's structural and functional scans was optimized using a FLAIR scan acquired with the same orientation as the functional scans.

Pre-processing

Pre-processing and analysis of structural and functional data was performed using FMRIB's Software Library (FSL version 4.1, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT/). We used BET (Brain Extraction Tool) for extraction of individual FLAIR and T1 weighted structural brain images and registered structural images to the MNI-152 template using FMRIB's Linear Image Registration Tool (FLIRT). FEAT (FMRI Expert Analysis Tool) was used for pre-processing and analysis of functional data. All individual subject scans underwent: motion correction using MCFLIRT; slice-timing correction using Fourier space time-series phase-shifting; spatial smoothing using a Gaussian kernel of FWHM 6mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 100 s); and Gaussian low-pass temporal filtering, with sigma = 2.8s. There was no significant difference between the two age groups in mean (old: .25, SE .03; young: .27, SE .02) functional displacement (motion), t(74) = -.551, p = .58.

Region of Interest (ROI) Connectivity Analysis

We performed connectivity analyses using three ROIs: left and right anterior temporal lobe (LATL, RATL) and left inferior frontal gyrus (LIFG). The LATL and RATL were created using clusters from Craddock's (Craddock, James, Holtzheimer, Hu, & Mayberg, 2011) parcellations; the LIFG mask was derived from Yeo's 17 network parcellation, and came from the 12th network. Any overlap between this LIFG site and frontal pole in the Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) was excluded in creating the final ROI mask. The mask extracted from the Yeo networks was resampled from 1mm to 2mm space and the masks from Craddock's parcellation was resampled from 4mm to 2mm. The masks were also smoothed with a gauss kernel of 1mm and binarized (Figure 3). Our ROI masks derived from resting state parcellations, rather than from anatomical boundaries, as we were testing for differences in RS connectivity and not for activity within isolated ROI's (Craddock, James, Holtzheimer Iii, Hu, & Mayberg, 2012).

Signal drop out is expected in the ATL, however, we aligned the FOV for each participant with the ATL's when acquiring scans in order to maximize the signal from this region. The tSNR for RATL (mean = 233, SD = 57), LATL (mean = 220, SD = 56) and LIFG (mean = 320, SD = 74) does differ significantly (LATL vs RATL: $t(75) = 4.1$, $p < .001$; RATL vs LIFG: $t(75) = -14.3$, $p < .001$; LATL vs LIFG: $t(75) = -15.2$, $p < .001$), however, there are no significant differences between the two age groups in tSNR for RATL (younger mean = 233 (SD = 60), older mean = 232 (SD = 55): $t(74) = .1$, $p = .9$) or LATL (younger mean = 225 (SD = 55), older mean = 215 (SD = 58), $t(74) = .7$, $p = .5$).

Average resting-state activity for each ROI was calculated per volume, and then subjected to functional connectivity analysis on a single-subject basis. The individual subject resting-state connectivity maps were then carried forward to a group analysis using FMRIB's Local Analysis of Mixed Effects, with a map threshold of $z = 3.1$ in order to define contiguous clusters, these were then corrected for family wise error ($p < .05$). We then ran t-tests on these maps to compare the old and young groups.

Methodological Limitations

This study used the standard MNI-152 template to register the younger and older participant brains. However, future studies should consider using the merged young and old-adult template (Buckner et al., 2004) to improve the registration process and reduce bias (the MNI-152 template is derived from young brains). Furthermore, no power analysis was conducted prior to data collection, as the sample size was largely dictated by the availability of older participants and grant funding. As such, the following results are exploratory in nature and need to be replicated in future studies using larger sample sizes.

Results

Behavioural Results

Our key analyses are based on response efficiency (median RT for accurate trials divided by accuracy), since this measure accounts for speed-accuracy trade-offs. We imputed (using each group mean) any behavioural outliers (2.5 SD outside of the mean for each age group separately), to minimise the impact of extreme values (no participants were outliers across all four task conditions; total number of imputed scores: old 7/160, young 3/164).

We used the NART and a shortened (18 questions) version of the Raven's Advanced Progressive Matrices (RAPM) test as covariates in our ANCOVA model to assess the contribution of

'intelligence' to any relationships between intrinsic connectivity and semantic cognition. Older individuals NART premorbid IQ estimate was significantly different (old: 119.32, young: 110.31; t(70) = -6.04, $p < .001$), consistent with a larger vocabulary, acquired over the lifetime, and consistent with the proposal that semantic representations are relatively unaffected by age (Hoffman, 2018a; Salthouse, 2004; Verhaeghen, 2003). However, while semantic representations remain stable, executive control processes become less efficient with age; older individuals performed less well than young adults on the RAPM (old: 36%, young 59%; t(77) = 6.54, $p < .001$).

Older individuals did not show the more efficient semantic retrieval for picture tasks seen in younger adults (see Figure 1, Table 2). This difference between age groups could not be attributed to vocabulary size or executive control, since the age by modality interaction remained largely unchanged when RAPM or NART scores were included as a covariate (controlling for RAPM: F(1, 76) = 5.74, $p = .019$; controlling for NART: F(1, 69) = 3.73, $p = .057$).

In addition, older adults showed a larger effect of strength of association than younger adults, reflecting less efficient semantic control (Hoffman, 2018a, 2018b). The effect of strength of association interacted significantly with RAPM (F(1, 76) = 7.16, $p = .009$) and the inclusion of this task as a covariate explained the age difference on this task (association strength by age with RAPM as a covariate: F(1, 76) = .58, $p = .45$), confirming the relationship between executive capacity and the ability to discern distant semantic relationships (Figure 1, Table 2).

	RAPM			NART		
	df	F	Sig.	df	F	Sig.
Association Strength	1,76	55.51	<.001**	1,69	1.73	0.19
Association Strength x Intelligence	1,76	7.16	0.009**	1,69	0.26	0.61
Association Strength x Age	1,76	0.58	0.45	1,69	4.81	0.032**
Modality	1,76	4.03	0.048**	1,69	0.77	0.38
Modality x Intelligence	1,76	0.16	0.69	1,69	0.37	0.54
Modality x Age	1,76	5.74	0.019**	1,69	3.73	0.057*

Table 2: ANCOVA results for behavioural manipulations. **$p < .05$, *$p < .1$.

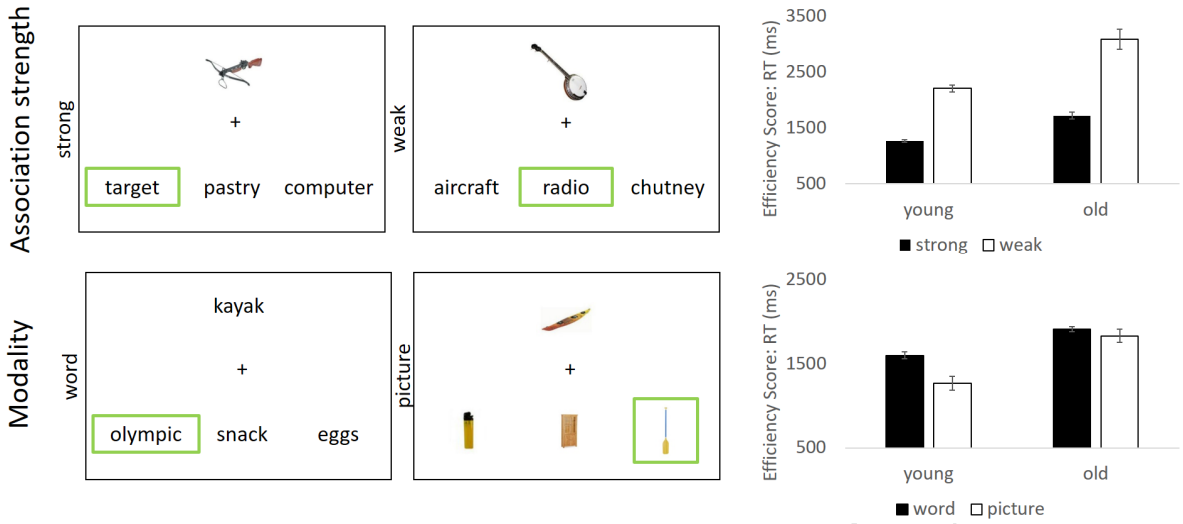

Figure 1: Task conditions for association strength (top) and modality (bottom), target highlighted in green; efficiency scores (RT/ACC) for both manipulations and age groups. Error bars indicate standard error of the mean.

Intrinsic Connectivity

We seeded three brain areas involved in semantic cognition, LATL, RATL and LIFG. The intrinsic connectivity of these areas was largely similar across the two age groups, consistent with a recent meta-analysis that found mostly comparable activation across young and old populations on semantic tasks, with some subtle differences (Figure 2; Hoffman & Morcom, 2018). For these seeds, there were several clusters reflecting stronger connectivity in younger than older adults, but not the reverse.

The analysis revealed weaker connectivity from RATL and LATL to other default mode network (DMN) regions in medial prefrontal cortex (mPFC) in older adults (Figure 3). Younger participants exhibited greater intrinsic connectivity from RATL to right mPFC (BA 10; Figure 3). Similarly, older adults had weaker LATL connectivity to dorsolateral medial prefrontal cortex (BA 9; Figure 3; this partly overlapped with the mPFC cluster identified using the RATL seed; Supplementary Figure S1). There was also reduced LATL connectivity to LIFG in older adults (extending across the whole of LIFG, with the peak in BA 47/pars orbitalis; Figure 3), in a region associated with executively demanding semantic tasks (e.g., Badre & Wagner, 2007; Krieger-Redwood, Teige, Davey, Hymers, & Jefferies, 2015; Noonan et al., 2013; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2012). Further inter-network reductions in connectivity were seen between the frontoparietal and the ventral attention networks for older individuals, compared to the younger group: the LIFG seed, which sits in the frontoparietal network, showed reduced connectivity to insular cortex extending into left superior temporal cortex (BA 22; Figure 3), in the ventral attention network.

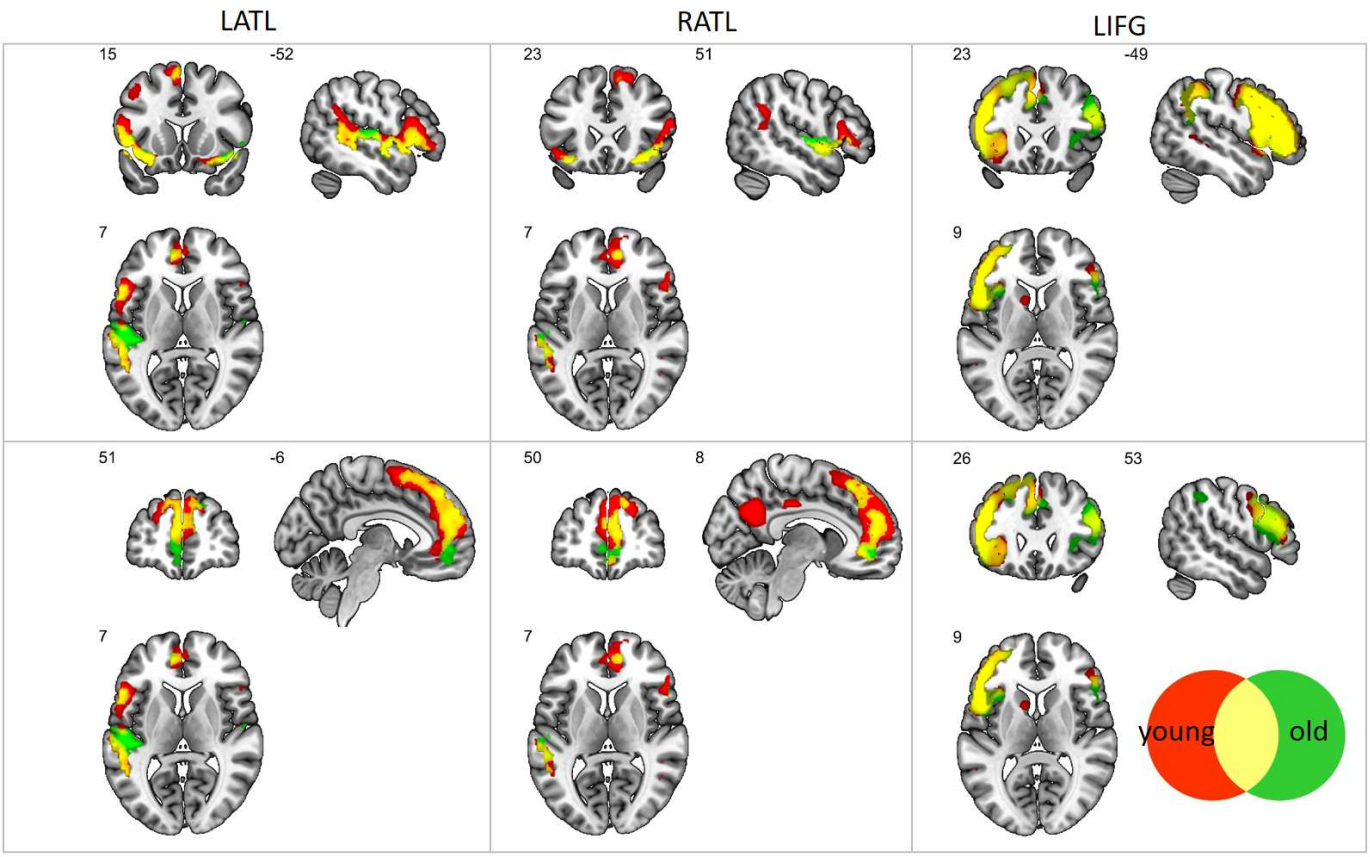

Figure 2: Connectivity from each seed region for both age groups.

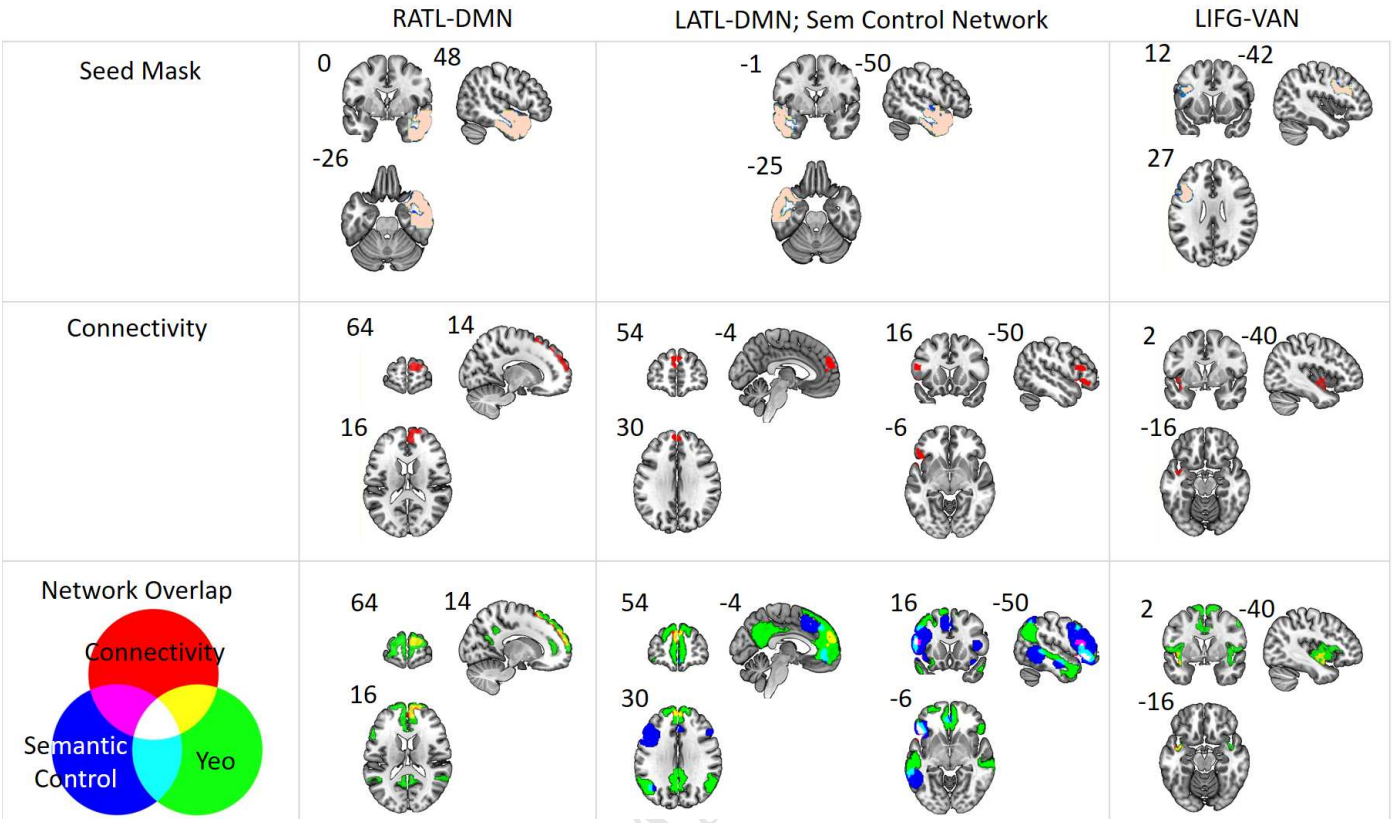

Figure 3: Top row shows the three seed masks; Connectivity row shows the significant younger>older resting state connections for each seed. The bottom row shows the seed connectivity overlaid with the default mode network (DMN; RATL, LATL connectivity; Yeo et al., 2011), the ventral attention network (VAN; LIFG connectivity; Yeo et al., 2011), and the semantic control network (LATL connectivity; Noonan et al., 2013). LATL was the only seed region that connected to two separate sites, therefore this site has two images per connectivity row.

The Interaction of Brain, Behaviour and Age

Next we assessed whether the weaker task performance of older adults, compared to younger adults, was associated with age-related differences in intrinsic connectivity, by performing six separate ANCOVAs to test for effects of (i) modality (3 ANCOVAs) and (ii) association strength/difficulty (3 ANCOVAs). The three ANCOVAs per manipulation (modality, association strength) tested the robustness of our findings, by demonstrating (i) the effect without controlling for intelligence/NART, (ii) controlling for NART, (iii) controlling for RAPM. Connectivity outliers (above/below 2.5SD) were imputed (using each group mean) within each age group (a total of 3 imputations across all participants). We means-centred the connectivity scores and behavioural scores by age group. We modelled the effects of age, behaviour and brain as a three-way interaction. This three-way interaction was modelled with NART and RAPM entered as covariates in separate models (see Table 3). Each ANCOVA (2 x 2 x 3) tested effects of task (2: picture/word *or* strong/weak association), by age (2: old/young), by brain (3: mean cope scores from the clusters that significantly connected to RATL/LATL/LIFG more for younger than older participants; these were entered into the model as covariates). NART and RAPM scores did not interact significantly with intrinsic connectivity for any of the clusters included in this study (Supplementary Table S1).

To interrogate the results of the large 2 (manipulation) x 2 (age) x 3 (brain) interactions, we conducted a further 6 ANCOVAS per age group. As with the large scale ANCOVA these tested for interactions between our two manipulations (modality, association strength) and connectivity. The separate ANCOVAs were used to capture any effects (i) without controlling for intelligence/NART, (ii) controlling for NART, (iii) controlling for NART and RAPM.

Our modality manipulation interacted significantly with RATL-mPFC connectivity ($F(1, 57) > 5.58$, $p < .02$), regardless of age. Low RATL-mPFC connectivity was associated with poorer performance on verbal semantic judgements (partial correlation controlling for LATL connectivity, LIFG connectivity, and RAPM: $r = -.19$, $p = .05$, one-tailed; Figure 4), but there was no such relationship for picture semantic judgements ($r = .06$, $p = .32$, one-tailed; Figure 4). The magnitude of this effect also differed across age groups (modality by age by RATL; $F(1, 57) > 4.15$, $p < .05$). Separate ANCOVAs on the individual age groups revealed a significant modality by RATL-mPFC connectivity interaction in older participants ($F(1, 29) > 5.51$, $p < .05$; Figure 4), but not in the younger age group ($F(1, 28) < .6$, $p > .44$; Figure 4). Stronger intrinsic coupling of RATL to mPFC preserves semantic access for words as we age, but does not mitigate the decline in semantic access for pictures that is seen in older adults (Figure 4; Table 3 and 4).

The effect of strength of association did not interact with connectivity for any of the three seeds ($F(1, 57) < 2.4$, $p > .13$; Figure 4, Table 3). However, there was a significant interaction of association strength by age by RATL-mPFC connectivity (RAPM: $F(1, 64) = 4.98$, $p = .029$; NART: ($F(1, 57) = 3.47$, $p = .068$; Figure 4, Table 3). Separate ANCOVAs on the individual age groups revealed an association strength by RATL interaction approaching significance for the older group irrespective of intelligence and vocabulary size ($F(1, 28) > 2.8$, $p \leq .1$; Figure 4, Table 3), but not for the young age group ($F(1, 28) < 1.4$, $p > .25$; Figure 4, Table 3). This interaction reflected better performance on both strong and weak associations in the younger group regardless of brain connectivity, while increased coupling between rATL and mPFC in older adults interfered with the ability to discern weak associations (semantic control; Figure 4; Table 3 and 4). Consequently, rATL to mPFC connectivity supports verbal semantic access in older adults but at the cost of poorer control over semantic retrieval.

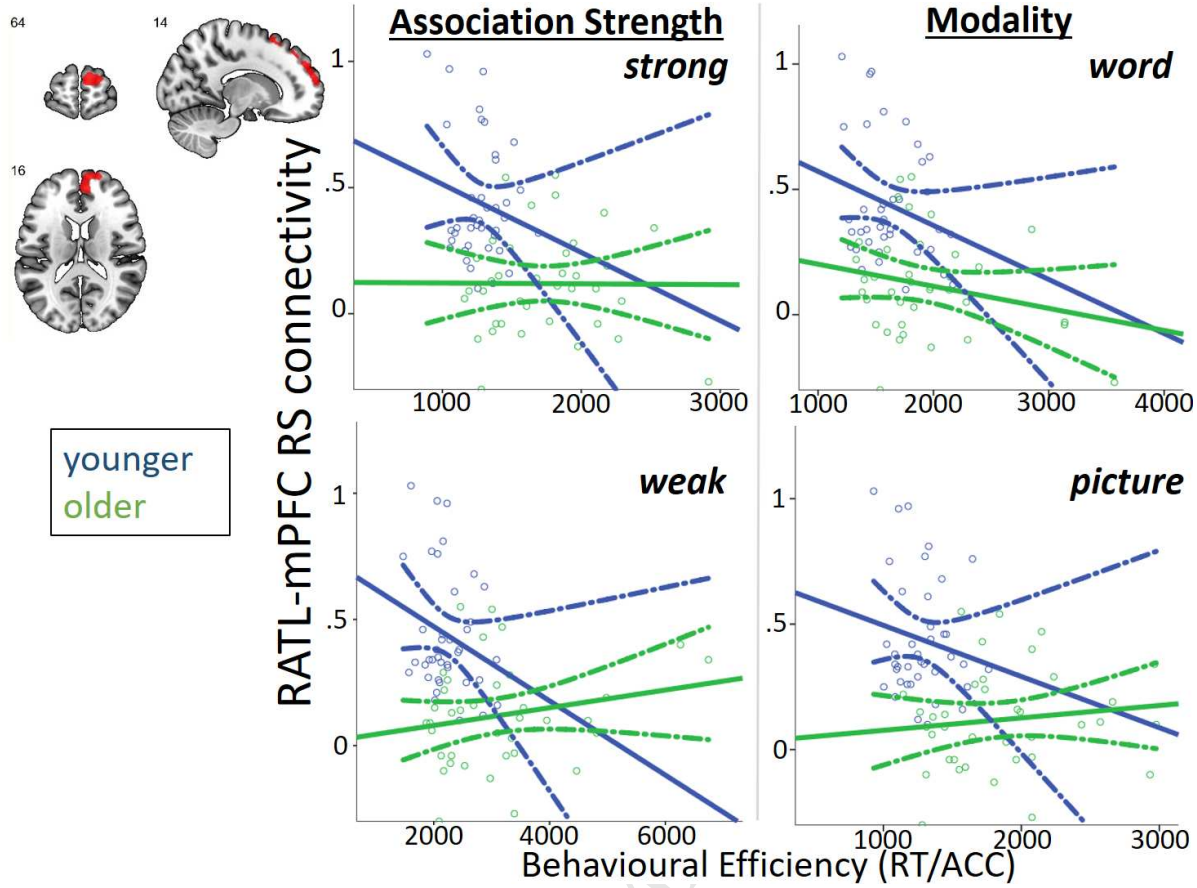

Figure 4: RATL-mPFC connectivity – behaviour (efficiency scores RT/ACC) interactions graphed by age (cf. Tables 3 and 4). RATL-mPFC connectivity shown in red on the brain images.

	Modality									Association Strength								
				NART			RAPM						RAPM			NART		
	df	F	Sig.	df	F	Sig.	df	F	Sig.	df	F	Sig.	df	F	Sig.	df	F	Sig.
Manipulation	1,68	0	0.987	1,57	0.54	0.46	1,64	0.61	0.44	1,68	0.041	0.84	1,64	6.1	0.016*	1,57	0.12	0.73
Manipulation x Age	1,68	0.029	0.865	1,57	0.15	0.70	1,64	1.02	0.32	1,68	0.008	0.93	1,64	0.6	0.43	1,57	0.17	0.68
Manipulation x RATL	1,68	5.919	0.018*	1,57	5.58	0.022*	1,64	7.26	0.009*	1,68	1.805	0.184	1,64	2.4	0.13	1,57	2.28	0.14
Manipulation x LATL	1,68	0.122	0.728	1,57	0.04	0.85	1,64	0.02	0.90	1,68	0.133	0.716	1,64	0.0	0.96	1,57	0.02	0.90
Manipulation x LIFG	1,68	0.519	0.474	1,57	0.25	0.62	1,64	0.03	0.86	1,68	1.529	0.22	1,64	2.0	0.16	1,57	0.45	0.51
Manipulation x Age x RATL	1,68	3.162	0.08^{+}	1,57	4.15	0.046*	1,64	4.20	0.044*	1,68	4.333	0.041*	1,64	5.0	0.029*	1,57	3.47	0.068^{+}
Manipulation x Age x LATL	1,68	0.825	0.367	1,57	0.26	0.61	1,64	0.49	0.49	1,68	0.006	0.939	1,64	0.1	0.75	1,57	0.04	0.85
Manipulation x Age x LIFG	1,68	1.294	0.259	1,57	0.33	0.57	1,64	0.39	0.54	1,68	0.698	0.406	1,64	1.4	0.24	1,57	0.50	0.48
Manipulation x Intelligence				1,57	0.53	0.47	1,64	0.96	0.33				1,64	8.0	0.006*	1,57	0.12	0.73
Manipulation x Age x Intelligence				1,57	0.16	0.69	1,64	1.48	0.23				1,64	2.2	0.15	1,57	0.17	0.69

Table 3: ANCOVA models for behaviour x age x brain, with intelligence as additional covariates. Six models were run: Modality (2: word/picture) x Age (2: young/old) x Brain (3: RATL, LATL, LIFG; entered as covariates) this model was run without NART and RAPM, and with NART as a covariate and separately with RAPM as a covariate; Association strength (2: strong/weak) x Age (2: young/old) x Brain (3: RATL, LATL, LIFG; entered as covariates) this model was run without NART and RAPM, and with NART as a covariate and separately with RAPM as a covariate. Significant results are denoted by: * $p < .05$, + $p < .1$.

		Modality									Association Strength								
					RAPM			NART						RAPM			NART		
		df	F	Sig.	df	F	Sig.	df	F	Sig.	df	F	Sig.	df	F	Sig.	df	F	Sig.
Young	Manipulation	1,35	0.0	0.8	1, 34	0.0	0.8	1, 28	1.3	0.3	1,35	0.0	0.9	1, 34	4.9	0.034*	1, 28	1.3	0.3
	Manipulation x RATL	1,35	0.6	0.4	1, 34	0.6	0.4	1, 28	0.1	0.7	1,35	1.5	0.2	1, 34	1.4	0.3	1, 28	0.4	0.6
	Manipulation x LATL	1,35	0.5	0.5	1, 34	0.5	0.5	1, 28	0.1	0.7	1,35	0.6	0.4	1, 34	0.4	0.5	1, 28	0.3	0.6
	Manipulation x LIFG	1,35	0.2	0.7	1, 34	0.2	0.6	1, 28	0.0	0.9	1,35	0.3	0.6	1, 34	0.1	0.7	1, 28	0.0	1.0
	Manipulation x Intelligence				1, 34	0.1	0.8	1, 28	1.2	0.3				1, 34	5.0	0.032*	1, 28	1.2	0.3
Old	Manipulation	1,33	0.0	0.9	1, 30	1.3	0.3	1, 29	0.0	0.8	1,33	0.0	0.9	1, 30	3.8	0.062^{+}	1, 29	0.0	1.0
	Manipulation x RATL	1,33	4.7	.04*	1, 30	5.5	0.026*	1, 29	5.6	0.025*	1,33	2.7	0.1^{+}	1, 30	3.0	0.094^{+}	1, 29	2.8	0.103^{+}
	Manipulation x LATL	1,33	0.4	0.5	1, 30	0.2	0.7	1, 29	0.1	0.7	1,33	0.0	0.9	1, 30	0.0	0.9	1, 29	0.0	1.0
	Manipulation x LIFG	1,33	1.1	0.3	1, 30	0.2	0.7	1, 29	0.4	0.5	1,33	1.2	0.3	1, 30	1.8	0.2	1, 29	0.5	0.5
	Manipulation x Intelligence				1, 30	1.3	0.3	1, 29	0.0	0.8				1, 30	4.1	0.051*	1, 29	0.0	1.0

Table 4: Separate ANCOVA models by age for behaviour x brain, with and without intelligence as additional covariates. Modality (2: word/picture) x Brain (3: RATL, LATL, LIFG; entered as covariates) this model was run without NART and RAPM, and with NART as a covariate and separately with RAPM as a covariate; Association strength (2: strong/weak) x Brain (3: RATL, LATL, LIFG; entered as covariates) this model was run without NART and RAPM, and with NART as a covariate and separately with RAPM as a covariate. Significant results are denoted by: * $p < .05$, + $p \leq .1$.

Discussion

The older participants in our study outperformed their younger counterparts on tests of vocabulary size (i.e., NART), but younger participants were faster and more accurate in semantic tasks tapping the flexible retrieval of conceptual knowledge. We were able to link this behavioural dissociation to age-related changes in intrinsic neural activity at rest, particularly connectivity between right ATL and mPFC within the DMN. Younger adults demonstrated higher intrinsic connectivity from RATL to mPFC at rest than older adults, and this was linked to better performance on verbal vs. picture semantic tasks, but they showed no relationship between this pattern of connectivity and performance on more challenging weak association tasks. In contrast, for older participants, increased RATL-mPFC connectivity was related to relatively good access to semantic knowledge for words, yet poorer controlled retrieval of weak associations. These brain-behaviour results were not explained by changes in domain-general executive control (i.e., RAPM), or knowledge within the semantic store (i.e., NART).

There is a growing body of literature demonstrating reduced within network connectivity for older adults (Allen et al., 2011; Andrews-Hanna et al., 2007; Clapp et al., 2011; Grady et al., 2016; Grady et al., 2010; Hedden et al., 2009). We replicated these findings, demonstrating weaker resting-state connectivity for older adults, within networks, as well as between networks. First, older participants showed weaker connectivity from RATL to mPFC – i.e., between two sites which fell within the DMN. A similar change in connectivity has been previously linked to lower white matter volume and cognitive decline (Andrews-Hanna et al., 2007). Further reductions in connectivity between DMN regions were seen for older adults between LATL and left and right dorsolateral medial prefrontal cortex (partly overlapping with the mPFC site identified from the RATL seed). As noted by Euston, Gruber and McNaughton (2012), mPFC has been implicated in memory retrieval, cognitive control, self-referential tasks (Gusnard, Akbudak, Shulman, & Raichle, 2001) and emotion processing (Etkin, Egner, & Kalisch, 2011; Morgan, Romanski, & LeDoux, 1993). Connectivity differences identified from the LATL seed also extended into LIFG regions implicated in semantic control (e.g., target selection amongst semantic competitors, controlled retrieval of task-relevant meaning). Therefore, our LATL seed uncovered both within-DMN and between network connectivity reductions with age. We also seeded dorsal IFG (the peak site for semantic control) and found reduced connectivity with insula cortex within the ventral attention network, implicated in cognitive control (Robertson, Hiebert, Seergobin, Owen, & MacDonald, 2015). While our study demonstrated reduced within and between network connectivity; others have demonstrated the same reduced within network connectivity, but increased connectivity between networks - however, this increased connectivity does not confer a performance advantage, rather it may reflect increased 'blurring' across systems (Chan, Park, Savalia, Petersen, & Wig, 2014). While our study did not find any increased between network connectivity for older adults, our smaller sample size may not have been well placed to be sensitive to increased activity across systems (for example, if there is greater individual variability with regard to between system connections).

All of these connectivity changes might contribute to cognitive decline in older adults, but only RATL-mPFC connectivity was found to relate differentially to semantic performance in older and younger adults in the current study. Connectivity between these DMN sites was linked to more efficient access to verbal semantics in both age groups, suggesting that RATL-mPFC connectivity plays a role in efficient verbal semantic processing. This pattern of connectivity appeared to be particularly critical for good verbal semantic performance in older adults. However, when the demands on semantic control increase, RATL-mPFC connectivity may interfere with the ability to discern distant semantic relationships, since older participants with increased RATL-mPFC

connectivity were less efficient at retrieving weak associations. It is unclear whether our results generalise to the DMN as a whole, or whether the relationship uncovered is specific to nodes within the DMN, such as RATL-mPFC. DMN regions are thought to be relevant to memory-guided cognition (Humphreys et al., 2015; Murphy et al., 2018; Murphy et al., 2017; Vatansever, Menon, Manktelow, Sahakian, & Stamatakis, 2015), and while deactivation of the DMN during executively demanding tasks has been linked to better performance (Kamp, Sorger, Benjamins, Hausfeld, & Goebel, 2018), this deactivation is reduced in semantic relative to other tasks (Wirth et al., 2011). Furthermore, healthy young adults effectively deactivate DMN in service of executively demanding tasks (e.g., Clapp et al., 2011; Kamp et al., 2018), while older adults are less able to decouple networks to meet externally generated demands (Andrews-Hanna et al., 2007; La et al., 2015; Persson et al., 2007). Therefore, while older adults regularly engage mPFC during access to semantic representations, this engagement may be detrimental when the need to exert control over these items arises (Reuter-Lorenz & Cappell, 2008; Spreng & Grady, 2010). If older individuals are less able to deactivate the DMN for externally generated executively demanding events, then those with heightened connectivity at rest may be at a disadvantage when it comes to focussed semantic task performance. This interpretation is in line with studies that have found that less deactivation of DMN for older than younger individuals results in poorer semantic performance on semantic classification tasks (Lustig et al., 2003). Furthermore, Seghier and Price (2012) postulate that, in young adults, mPFC is deactivated when the demands on semantic cognition increase, with reallocation of resources to other areas within the DMN (e.g., IPL) and other networks (e.g., semantic control network). Our results align well with this idea, given that those older individuals with increased RATL-mPFC connectivity benefitted from rapid access to verbal semantic representations, but were also less able to discern challenging semantic associations, suggesting they may not be deactivating efficiently when the task demands change. Several studies have demonstrated functional dissociations within the DMN (Humphreys et al., 2015; Seghier & Price, 2012), and some patterns of coupling within this network might advantage semantic cognition in older adults, while others might be detrimental, and this balance may shift based on the demands placed on simple vs. controlled semantic cognition; more research is needed to investigate this possibility.

Furthermore, Spreng and colleagues have also noted this dissociation in ageing with an increased conceptual knowledge base, but reduced capacity for controlled cognition and have recently proposed a model to account for this trade off (DECHA; Spreng et al., 2018; Spreng & Turner, 2019). As individuals age, there is a shift towards a greater reliance on semantic cognition (or, prior knowledge) as task demands increase. This shift in cognition is mirrored by functional connectivity showing effective and flexible modulation between executive and DMN networks in younger adults, but poorly regulated DMN connectivity with executive regions in older adults. As task demands increase, younger adults benefit from efficient use of control systems, while older adults rely on crystalised intelligence – in our study, older adults with increased within-DMN activity performed less well as task demands increased, and this may reflect this over-reliance on prior knowledge and an inability to decouple from the DMN to control regions in service of the task.

In conclusion, this study aimed to assess how key nodes of the semantic network differ in their intrinsic connectivity with age, and how these differences may relate to their use of semantic knowledge. The older individuals showed reduced connectivity between right ATL and mPFC compared with younger adults, and this reduction in connectivity was correlated with preserved verbal semantic performance but poorer controlled semantic retrieval. Our study is consistent with research suggesting the DMN may interfere with the successful completion of goal directed semantic tasks in older adults, who have a depleted capacity for cognitive control.

Acknowledgements:

This study was supported by the Dunhill Medical Trust (Project ID - R422/0515) and funding from the European Research Council (Project ID: 771863 - FLEXSEM and Project ID: 646927-WANDERINGMINDS).

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- Older adults have a greater vocabulary size, but with reduced semantic control
- Within DMN connectivity (RATL to mPFC) for access to verbal (not picture) semantics
- Increased RATL-mPFC connectivity linked to reduced semantic control in older adults

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